Application note 2017.01

Particle size analysis related to dissolution and crystallisation studies

It is well known that the solubility of a drug is influenced by several properties including pH, temperature and lattice energy of the solute. Dissolution, the rate at which a solute enters a dissolving medium, is also influenced by properties which are specific to the manufacturing process. One key property is the surface area of the solute and by inference, particle size. Particle size is therefore of key importance in predicting how a specific drug or excipient will behave. Measuring and controlling particle size and other properties enables control of the dissolution properties of a dosage form. This application note describes how laser obscuration time (LOT) and image analysis can be used to correlate the physical characteristics of solid dispersions with dissolution behaviour. Additionally, a further example illustrates how laser obscuration time can be used to monitor the growth of crystals in real time during crystallisation.

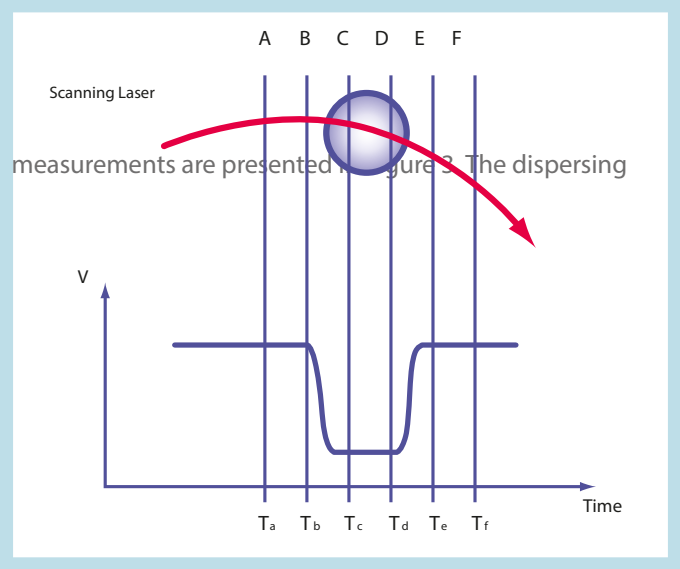

Figure 1. Particle Size Measurement using LOT

The laser obscuration time method measures the attenuation of a focussed, rotating laser beam as it interacts with a particle to determine the chord length. The attenuation profile is processed to reject off-centre and out-of focus particle interactions. This methodology is implemented in the EyeTech particle size and shape analyser which yields both number and volume distributions.

Laser Obscuration Time

Particle size measurements made using the laser obscuration time technique have the advantage of not requiring the optical properties of the particles or suspending medium to be known. This gives a valuable approach to monitoring particles which comprise more than one component (such as solid dispersions) or where the dispersing medium may change in composition (for example during crystallisation). The method determines the transition time of a rotating laser beam crossing a particle, and does not assume that all particles are spheres. It measures the size of individual particles and generates a histogram showing the numbers of particles in each size class observed. This permits the measurement of small particles in the presence of larger and growing particles. The LOT measurement technology is incorporated in the EyeTech instrument, which also includes digital image analysis to derive information on particle shape. The EyeTech was used to investigate physical properties of the drugs discussed in this application note. Figure 1 illustrates the operating principle of LOT measurement.

Solid Dispersions

Nine preparations of HPMCAS and felodipine (3:1 ratio) were prepared as solid dispersions using nine different spray drying conditions*. Outlet temperature, nozzle pressure and feed concentration were varied in the experimental design in order to generate a powder suitable for direct compression. The powder dissolution profiles of these preparations were determined using a SiriusT3 autotitrator at pH 7.0 and the results are presented in Figure 2. The solid dispersions demonstrate significant variation in dissolution characteristics with Tests 1 and 2 dissolving more rapidly and to a greater extent than the other dispersions. The particle size distribution of each solid dispersion was measured using the EyeTech and summary statistics from these medium was isooctane with a small amount of additive to achieve good dispersion of the particles. Sonication was applied for 20 seconds to assist with dispersion.

*The solid dispersions were supplied by Shin-Etsu Chemical Co. Ltd. and their assistance in this study is gratefully acknowledged.

Application note 2017.01

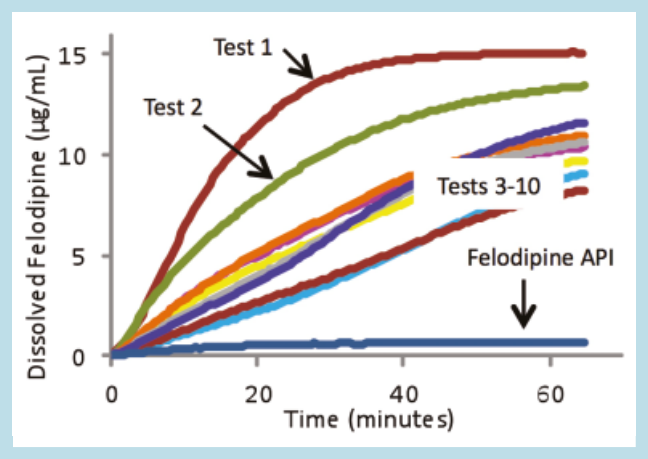

Figure 2. Powder dissolution profiles for felodipine/HPMCAS solid dispersions at pH 7.0

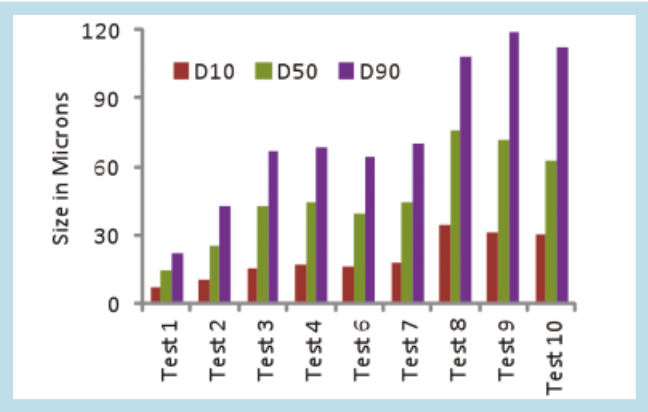

Figure 3. Particle size summary data generated using LOT for nine solid dispersions, measured after sonication. "D10" signifies that 10% of the total number of particles were smaller than the D10 value; "D50" is the median value and 90% of particles have a particle size less than the D90 value.

The two solid dispersions which showed the most significant dissolution enhancement were determined to have the smallest particle size as shown in Figure 3. Conversely, the dispersions which showed the smallest solubility enhancement had the largest particle sizes. These particle data were corroborated by image analysis measurements on the Insight and two example images are shown in Figures 4 and 5.

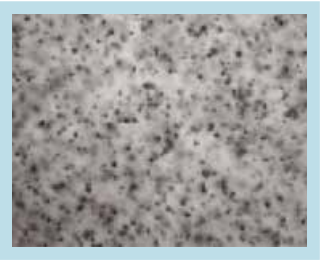

Figure 4. Dispersion from Test 1: fast dissolution

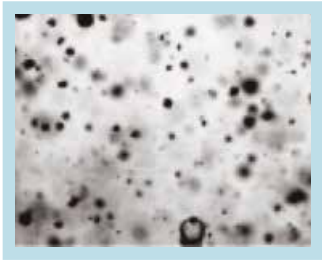

Figure 5. Dispersion from Test 8: slow dissolution

Piroxicam Crystallisation

The crystallisation of piroxicam was studied using the Eye. Crystallisation was initiated by changing the pH of a basic solution of piroxicam through the addition of 0.5M HCl. Figure 6 shows the particle size trend data by plotting the D10, D50 and D90 percentiles of the distributions following acidification using LOT size measurement. Over time, the number of large particles clearly increases reflecting crystal growth and the fusing of crystals. Particle size frequency distributions at 60, 300 and 600s are shown in Figure 7 accompanied by images captured by the instrument at these time points.

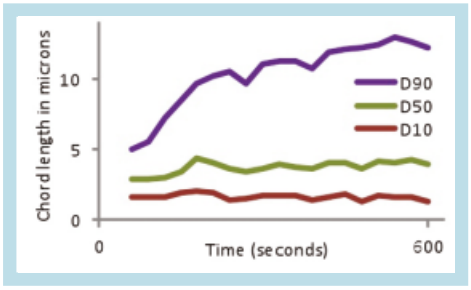

Figure 6. Particle size trend data for the crystallisation of piroxicam (number distribution)

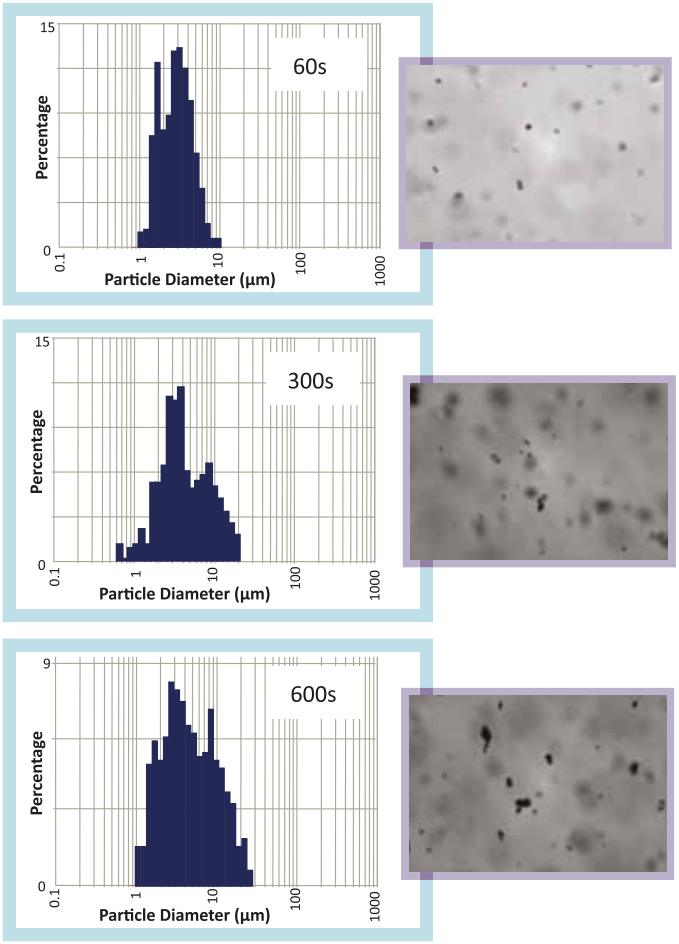

Figure 7. Particle size distributions and images for piroxicam crystallisation at 60, 300 and 600s